Cooperative Planning Grant for Cancer Disparities Research Partnership Program

The National Cancer Institute (NCI) invites cooperative planning grant applications to develop models to reduce significant negative consequences of cancer disparities seen in certain U.S. populations. This grant will support the planning, development, and conduct of radiation oncology clinical research trials in institutions that care for a disproportionate number of medically underserved, low-income, ethnic, and minority populations but have not traditionally been involved in NCI-sponsored research. The grant will also support the planning, development, and implementation of nurturing partnerships between applicant institutions and committed, experienced institutions actively involved in NCI-sponsored cancer research.

The NCI is strongly committed to reducing cancer-related health disparities across the cancer control continuum from prevention to end of life. The NCI supports research to understand the complex causes of disparities in cancer risk, incidence, and mortality, including socioeconomic, cultural, environmental, institutional, behavioral, biological, and other contributing factors seen in the health care delivery system. The overall goal is to understand the causes of health disparities and to develop effective interventions to eliminate these disparities that result in significant negative outcomes.

The populations targeted by this cooperative planning grant tend to access the health care system in the advanced stages of their disease. Because of this, radiation oncology usually represents a major treatment alternative. Therefore, the field of radiation oncology offers a unique opportunity to explore ways to reduce the significant negative consequences of cancer-related health disparities.

Institutions, with the necessary resources, mentoring, and supportive partnership with an experienced and committed research institution, represent an opportunity for conducting and expanding participation in clinical trials developed for radiation oncology and combined modality therapy as well as culturally and societally related research important to the understanding of cancer-related health disparities. However, health care institutions providing cancer services to a disproportionate number of medically underserved, low-income, and/or minority populations, whether urban or rural, often are not linked to the national cancer research enterprise as effectively as they could be and often struggle to maintain state-of-the-art cancer care. Radiation oncologists in these institutions have difficulty starting, developing, and sustaining research programs either independently or collaboratively. Thus, the populations primarily served by these institutions do not readily benefit from the rapid progress being made in cancer research in radiation oncology, and may bear an unequal burden of disease as a result.

It is necessary to address the low involvement in cancer research of health care institutions predominantly serving populations who experience the worst consequences of cancer-related health disparities. The increased involvement of these institutions is needed to develop a stronger national cancer research effort aimed at understanding the disparities of cancer incidence and mortality in those populations. This cooperative planning effort is dedicated to developing stable, long-term radiation oncology clinical research trials, programs, and partnerships to increase the participation of applicant institutions in the nation's cancer research enterprise.

The four overall objectives and scope of this RFA are to solicit cooperative planning grants that 1) build and stabilize independent and collaborative clinical research capabilities of institutions providing radiation oncology care to populations experiencing the negative consequences of cancer-related health disparities; 2) increase the number of clinical scientists engaged in radiation oncology research by providing access to and participation in clinical trials with the target populations; 3) improve the effectiveness of the applicant institution and its partner institution in developing and sustaining activities focused on radiation oncology clinical research trials and mortality and morbidity in cancer among the target populations, continuing past the life of this grant; and 4) establish priorities for and initiate stable, long-term collaborations and partnerships that will strengthen competitive cancer research, research training and career development, education, and outreach capabilities at both the applicant institution and the partner institution that address problems and issues relevant to the disproportionate cancer incidence and mortality.

All approaches to planning are encouraged, as long as they address the following essential features: a focus on cancer disparities, radiation oncology clinical research, institutional commitment, organizational capabilities, facilities, and interdisciplinary coordination and collaboration.

The NCI plans to commit approximately $2.8 million in direct costs in fiscal year 2003 to fund up to four new grants in response to this RFA. Applicants may request a project period of up to five years and an annual budget for direct costs of up to $400,000 per year over five years, excluding one-time capital costs expended in the first year. Awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. The total project period for applications submitted may not exceed five years. The anticipated award date is 20 September 2003.

Applications will only be accepted from health care institutions accredited by the Joint Commission on Accreditation of Health Organizations or free-standing cancer centers accredited by a nationally recognized accrediting body such as the American College of Radiology (either in the United States or in territories under U.S. jurisdiction) that have letters of commitment from potential partners that are NCI-designated cancer centers, RTOG-participating institutions, or other NCI-sponsored cooperative group participating institutions wishing to develop comprehensive partnerships with the applicant institution.

Applications must be prepared using the PHS 398 grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. The deadline for letters of intent is 20 February 2003, with final applications due 20 March 2003. More information on this RFA is available online at http://grants1.nih.gov/grants/guide/rfa-files/RFA-CA-03-018.html.

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Continued Development and Maintenance of Bioinformatics/Computational Biology Software

Biomedical research laboratories occasionally create software to solve a problem the laboratory faces. These software packages sometimes evolve into a well-designed system that can be easily extended and that is useful to a much broader community beyond the members of the originating laboratory. The goal of this PA is to support the continued development, maintenance, testing, and evaluation of existing software. The proposed work should apply best practices and proven methods for software design, construction, and implementation to extend the applicability of existing bioinformatics/computational biology software to a broader biomedical research community.

This initiative pertains to bioinformatics/computational biology software that is recognized to perform an important function in furthering biomedical research. The software should perform reliably and precisely according to the computing demands of end users. The algorithms that are employed by the software should be well documented, as should be the underlying assumptions of these algorithms to prevent potential misuse.

Contemporary software must be fully documented and easy to modify and extend. Defects that arise in any software must be correctable with limited effort. As the needs of a community of users change, the software that supports their research efforts must be easily modified. Reparability and evolvability are particularly important because the scientific discovery process is open-ended and ever-changing. Interoperability and portability are also a major concern. Where appropriate, software applications should operate on a variety of platforms employing different operating systems.

Awards made under this PA will support continued software development, evaluation, and testing of preexisting bioinformatics/computational biology software for data management and analysis, computational biology, and modeling and simulation. Support will be provided for porting software to new platforms and operating systems as well as the costs associated with maintaining the software as existing operating systems change. The proposed software should not substantially duplicate another software package that is already in wide use.

This PA will use the NIH R01 award mechanism as well as competitive supplements to existing R01, R33, P01, P41, P50, and P60 grants that have already been awarded by one of the participating institutes or centers. Applications for competitive supplements cannot extend beyond the parent project period of performance, and the principal investigator must be the same.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines, available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

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Genetic Architecture, Biological Variation, and Complex Phenotypes

This PA updates PA-98-078, "Genetic Architecture of Complex Phenotypes." The purpose of this PA is to solicit applications for new studies on genetic variation and the architecture of complex phenotypes. It restates the interest of several components of the NIH in studies of the underlying causes and architecture of complex phenotypes, including human diseases. It is motivated by the amount and complexity of biological data that are being generated and by the understanding that complex phenotypes involve many genetic components that evolve in a variety of environments.

Complex phenotypes are those that exhibit familial clustering, which may mean that there is some genetic component, but that do not occur in Mendelian proportions in pedigrees. Complex phenotypes may be continuous in distribution (e.g., height or blood pressure), or they may be dichotomous (e.g., affected and not affected). The complexity arises from the fact that one cannot accurately predict the expression of the phenotype from knowledge of the individual effects of individual factors considered alone, no matter how well understood each separate component may be.

The past few decades of biological research using largely a reductionist approach have yielded vast amounts of data. In addition, genome sequencing projects, as well as structural and functional genomics initiatives, are producing data far more rapidly than scientists can analyze them and understand their implications to biology and to health. As overwhelming as the current data are, they are only the beginning. Protein structures, DNA sequences, and gene expression patterns vary among individuals, among species, among populations within a species, and across environments. It will soon be possible to utilize information on thousands of variable genetic sites to investigate the relationships among genotypes, phenotypes, and environments.

The term *genetic architecture* refers to the full range of genetic effects on a trait; however, when studying variation on such a large scale, it is especially important to consider the context or environments in which genetic variation arises, is selected, and is maintained. Genetic architecture is less a fixed property of the phenotype than a characteristic of a phenotype in a particular population. Genetic architecture is a moving target that changes according to gene and genotype frequencies, distributions of environmental factors, and such biological properties as age and sex.

Studies of variation or genetic architecture may employ a variety of conceptual approaches. A researcher may consider the combinatorial effects of many variable sites, whether the scale is within a gene or across a genome. Comparative genomics, where the goal is to identify patterns of variation among genomes, is also a productive way of identifying attributes of variation, such as which genomic regions are rapidly evolving. Another approach is to study variation related to biological levels of organization, such as DNA sequence, protein structure, metabolic pathways, cell dynamics, individual phenotype, and population characteristics. The following are typical of research areas targeted by this initiative:

Biological variation: Studies of genetic architecture have historically focused on associations of genotype and phenotype (e.g., between DNA markers and a disease). However, an organism is a unique consequence of both genes and environment and is created by complex interactions of multiple events and forces. How genes are expressed depends on their cellular, developmental, physiological, and environmental context. This initiative encourages research on biological variation and interactions such as 1) variation in basic biological systems, including sequences, structures, and pathways that direct metabolism and development; 2) variation in these systems within individuals, among individuals, among populations, and among species with the goal of learning how these complex systems interact and evolve; 3) determination of the extent to which genetic architecture is shared across populations and among species; 4) effects of admixture, population history, recombination, mutation, population structure, selection, and drift on the organization of variation; 5) collection and analysis of both new and existing data; 6) tools and models for identifying and measuring important contextual features; and 7) measuring the impact of context on biological data.

Evolution of genome properties: An emerging area of research focuses on how properties of genomes arise in evolutionary history. Such research has important consequences for understanding genome organization and for interpreting data on genetic and phenotypic variation. Such research could include the evolution of haplotypes, selection for genetic interactions, and the evolution of recombination and methylation patterns.

Extensions to other organisms: Many organisms have been studied for their value in agriculture or ecology. Thus, there is considerable information about the population structure, natural history, and genetics of these systems. It will be valuable to take advantage of this wealth of information to study variation in the natural settings in which it evolved.

Bioinformatics: The study of biological variation depends heavily on rich data sets; researchers need the ability to access many kinds of information (e.g., DNA sequence, protein structure, development, natural history, and phenotype) in organisms from different habitats, from different populations, and from different species. This initiative supports development of tools to help researchers use data from many databases to address research questions.

Improved dynamic modeling and statistical methods: Mathematical approaches to studying biological variation have changed little in several decades. There is a need to develop new dynamic models to illuminate how systems interact and evolve. Just as important, it is critical to study the nature of biological and mathematical assumptions of models and statistics. Tools for analyzing and interpreting data on the architecture of complex phenotypes should be developed in the context of real biological information. Areas of particular interest for this initiative include 1) implications and appropriate uses of different sampling strategies; 2) analytical tools to discover patterns of genotypic variation and their roles in conferring phenotype; 3) incorporation of data from new technologies; 4) development of robust methods that are compatible with real data (missing or incomplete data, typing errors, experimental errors); and 5) development of mathematical models based on empirical information, which includes such biological realities as epistasis, recombination, mutation, protein structure, cell biology, metabolic pathways, development, population history, and evolution.

Applications submitted in response to this PA will be accepted at the standard application deadlines, available at http://grants.nih.gov/grants/dates.htm. Complete information on this PA is available at http://grants1.nih.gov/grants/guide/pa-files/PA-02-110.html. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001), available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format.

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